Document Number 1

Entry 1 of 2 File: USPT Dec 8, 1998

US-PAT-NO: 5846929
DOCUMENT-IDENTIFIER: US 5846929 A

TITLE: Purification of type G botulinum neurotoxin and pharmaceutical compositions thereof
DATE-ISSUED: December 8, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Johnson; Eric A.	Madison	WI	N/A	N/A
Sugiyama; Hiroshi	Madison	WI	N/A	N/A
Malizio; Carl J.	Madison	WI	N/A	N/A

US-CL-CURRENT: 514/2; 435/68.1, 435/70.1, 435/70.3, 435/842, 514/21, 530/350, 530/412 , 530/413, 530/416, 530/417, 530/418, 530/825

CLAIMS:

We claim:
1. A type G botulinum neurotoxin having a molecular weight of about 144,000 daltons as determined by gel filtration and SDS-PAGE, said neurotoxin having a specific toxicity of between 1.0.times.10.sup.7 and 5.0.times.10.sup.7 LD.sub.50 /mg protein wherein the neurotoxin was obtained from Clostridium botulinum grown under anaerobic conditions.
2. A method of obtaining natural type G botulinum neurotoxin which comprises
(a) growing Clostridium botulinum strain 89 under anaerobic conditions in a suitable medium to obtain a culture broth having activity of between 3.0.times.10.sup.4 and 4.0.times.10.sup.4 LD.sub.50 /ml; and,
(b) isolating the neurotoxin by adding yeast RNA and adjusting pH of the broth to about 3.4 to precipitate a toxin complex, adding RNAase and treating the precipitated toxin by DEAE Sephadex ion exchange purification and PAPTG affinity chromatography to obtain the isolated neurotoxin,
wherein yield of the neurotoxin is between 9% and 11%.
3. A method of claim 2 in which the neurotoxin is activated with Endoproteinase Lys-C.
4. A method of obtaining type G botulinum neurotoxin which comprises
(a) growing Clostridium botulinum under anaerobic conditions in a suitable medium to obtain a culture broth having activity of >3.0.times.10.sup.4 and 4.0.times.10.sup.4 LD.sub.50 /ml; and,
(b) isolating the neurotoxin by adding yeast RNA and adjusting pH of the broth to precipitate a toxin complex, adding RNAse and treating the precipitated toxin by ion exchange purification and affinity chromatography to obtain the isolated neurotoxin,
wherein yield of the neurotoxin is between 9% and 11%.

Document Number 2

Entry 2 of 8 File: USPT Nov 17, 1998

US-PAT-NO: 5837265
DOCUMENT-IDENTIFIER: US 5837265 A

TITLE: Chemically-modified clostridiatoxin with improved properties
DATE-ISSUED: November 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Montal; Mauricio	La Jolla	CA	N/A	N/A
Ferrer-Montiel; Antonio	La Jolla	CA	N/A	N/A

US-CL-CURRENT: 424/239.1; 424/832, 514/2, 530/324

CLAIMS:

What is claimed is:
1. A Clostridium neurotoxin having tyrosine residues phosphorylated to have a negative charge, wherein the proteolytic activity and thermal stability of the neurotoxin are enhanced as compared to Clostridium neurotoxins in which negatively charged tyrosine residues are absent.
2. The neurotoxin according to claim 1 wherein the neurotoxin is a Clostridium botulinum neurotoxin.
3. The neurotoxin according to claim 2 wherein the neurotoxin is botulinum toxin A, botulinum toxin B, or botulinum toxin E.
4. The neurotoxin according to claim 1 wherein the neurotoxin is a Clostridium tetani neurotoxin.
5. A pharmaceutical composition comprising a Clostridium neurotoxin having tyrosine residues phosphorylated to have a negative charge, and a pharmaceutically acceptable carrier, wherein the proteolytic activity and stability of the neurotoxin are enhanced as compared to Clostridium neurotoxins in which negatively charged tyrosine residues are absent.
6. The pharmaceutical composition according to claim 5 wherein the neurotoxin is a Clostridium botulinum neurotoxin.
7. The pharmaceutical composition according to claim 6 wherein the neurotoxin is botulinum toxin A, botulinum toxin B or botulinum toxin E.
8. The pharmaceutical composition according to claim 5 wherein the neurotoxin is a Clostridium tetani neurotoxin.
9. A Clostridium neurotoxin wherein tyrosine residues therein are sulfated to have a negative charge, wherein further the proteolytic activity and thermal stability of the neurotoxin are enhanced as compared to Clostridium neurotoxins in which negatively charged tyrosine residues are absent.
10. The neurotoxin according to claim 9 wherein the neurotoxin is a Clostridium botulinum neurotoxin.
11. The neurotoxin according to claim 10 wherein the neurotoxin is botulinum toxin A, botulinum toxin B, or botulinum toxin E.
12. The neurotoxin according to claim 9 wherein the neurotoxin is a Clostridium tetani neurotoxin.
13. A pharmaceutical composition comprising a Clostridium neurotoxin wherein tyrosine residues therein are sulfated to have a negative charge, and a pharmaceutically acceptable carrier, wherein further the proteolytic activity and stability of the neurotoxin are enhanced as compared to Clostridium neurotoxins in which negatively charged tyrosine

compared to Clostridium neurotoxins in which negatively charged tyrosine residues are absent.

14. The pharmaceutical composition according to claim 13 wherein the neurotoxin is a Clostridium botulinum neurotoxin.

15. The pharmaceutical composition according to claim 14 wherein the neurotoxin is botulinum toxin A, botulinum toxin B or botulinum toxin E.

16. The pharmaceutical composition according to claim 13 wherein the neurotoxin is a Clostridium tetani neurotoxin.

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Document Number 4

Entry 4 of 8 File: USPT Feb 3, 1998

US-PAT-NO: 5714468
DOCUMENT-IDENTIFIER: US 5714468 A

TITLE: Method for reduction of migraine headache pain
DATE-ISSUED: February 3, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Binder; William J.	Pacific Palisades	CA	90272	N/A

US-CL-CURRENT: 514/14; 514/2

CLAIMS:

I claim:
1. A method for reduction of pain associated with a migraine headache in a mammal comprising administering a therapeutically effective amount of an invertebrate presynaptic neurotoxin in a pharmaceutically safe form to the mammal.
2. The method according to claim 1 wherein the neurotoxin is delivered to the face, cranium and neck.
3. The method according to claim 2 wherein the presynaptic neurotoxin is delivered to one or more of the frontalis, corrugator, procerus and bilateral temporal muscles.
4. The method according to claim 2 wherein the presynaptic neurotoxin is also delivered to the mammal's back.
5. The method according to claim 1 wherein the presynaptic neurotoxin is administered by electromyographical injection into the muscle.
6. The method according to claim 1 wherein the presynaptic neurotoxin is administered by injection in the area of the neuromuscular junction.
7. The method according to claim 1 wherein the presynaptic neurotoxin is a Botulinum toxin.
8. The method according to claim 7 wherein the Botulinum toxin is Botulinim toxin A.
9. The method according to claim 1 wherein the presynaptic neurotoxin is a biologically active fragment of a proteinaceous toxin.
10. The method according to claim 9 wherein the biologically active fragment is the lbc fragment of the Tetanus toxin.
11. A method for reduction of symptoms associated with the onset or presence of a migraine headache in a mammal comprising administering a therapeutically effective amount of an invertebrate presynaptic neurotoxin in a pharmaceutically safe form to the mammal.
12. A method for reduction of pain associated with a migraine headache in a mammal comprising administering a therapeutically effective amount of an invertebrate presynaptic neurotoxin in a pharmaceutically safe form to the mammal by delivery of the presynaptic neurotoxin to an extramuscular site of the face, cranium or neck.
13. The method according to claim 12 wherein the neurotoxin is delivered to one or more target sites of the migraine headache pain experienced by the mammal.
14. The method according to claim 13 wherein the presynaptic neurotoxin is delivered to one or more of the frontal, temporal and suboccipital

areas of the face.
15. The method according to claim 12 wherein the presynaptic neurotoxin is administered by perivascular injection.
16. The method according to claim 12 wherein the presynaptic neurotoxin is administered by subcutaneous injection.
17. The method according to claim 12 wherein the presynaptic neurotoxin is a Botulinum toxin.
18. The method according to claim 17 wherein the Botulinum toxin is Botulinum toxin A.
19. The method according to claim 12 wherein the presynaptic neurotoxin is a biologically active fragment of a proteinaceous toxin.
20. The method according to claim 19 wherein the biologically active fragment is the Ibc fragment of the Tetanus toxin.
21. A method for reduction of symptoms associated with the onset or presence of a migraine headache in a mammal comprising administering a therapeutically effective amount of an invertebrate presynaptic neurotoxin in a pharmaceutically safe form to the mammal by delivery of the presynaptic neurotoxin to an extramuscular site in the face, cranium or neck.

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Document Number 5

Entry 5 of 8 File: USPT Dec 9, 1997

US-PAT-NO: 5696077
DOCUMENT-IDENTIFIER: US 5696077 A

TITLE: Pharmaceutical composition containing botulinum B complex
DATE-ISSUED: December 9, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Johnson; Eric A.	Madison	WI	N/A	N/A
Goodnough; Michael C.	Madison	WI	N/A	N/A
Borodic; Gary E.	Canton	MA	N/A	N/A

US-CL-CURRENT: 514/2; 424/184.1, 424/234.1, 424/247.1

CLAIMS:

What is claimed is:
1. A pharmaceutical preparation for use in inducing local, partial, titratable, muscle denervation in a patient, the preparation comprising: a frozen, dried sodium chloride-free preparation comprising C. botulinum type B neurotoxin complexed with botulinum-derived stabilizing proteins, the complex having a molecular weight as determined by gel filtration chromatography of from about 300 KD to about 450 KD, in admixture with a pharmaceutically acceptable protein excipient for maintaining the stability of the complex at concentrations of 10.sup.4 mouse LD.sub.50 units per milliliter or less, which, when reconstituted in aqueous solution, retains at least 75% of its toxic activity.
2. The pharmaceutical preparation of claim 1 characterized as having a pH between 5.0 and 7.3 when reconstituted.
3. The pharmaceutical preparation of claim 1 which, when reconstituted retains at least 90% of its toxic activity.
4. The pharmaceutical preparation of claim 1 wherein the protein excipient is selected from the group consisting of albumin and gelatin.
5. The pharmaceutical preparation of claim 1 wherein at least one of said stabilizing proteins comprises a red blood cell agglutinating factor coexpressed with the neurotoxin by C. botulinum.
6. The pharmaceutical preparation of claim 1 substantially free of bacterial proteins other than said neurotoxin and stabilizing proteins.
7. A method of selectively, partially, temporarily, chemically denervating a volume of muscle in a mammal, the method comprising the steps of:
reconstituting the frozen, dried preparation of claim 1 to form a toxically active aqueous solution;
injecting into a point within said muscle volume a dose of the reconstituted composition sufficient to reduce involuntary contraction thereof while permitting continuing voluntary contraction; and
permitting said dose to diffuse throughout said muscle volume to induce partial denervation thereof.
8. The method of claim 7 further comprising:
injecting individual doses of said composition into sites spaced apart within said predetermined volume of muscle, the spatial relationship of

the sites being sufficient to at least partially denervate the entirety of said volume.
9. The method of claim 7 wherein said volume of muscle comprises a single muscle, the method comprising injecting a unit dose of said pharmaceutical, into an innervating zone of said muscle, and permitting said dose to diffuse through said innervating zone to induce partial denervation of the entirety of said muscle.
10. A method of decreasing spasm and involuntary contraction in a muscle of a patient induced by pathologic neural stimulation, the method comprising the steps of reconstituting the frozen, dried preparation of claim 1 and injecting into at least a portion of an innervation zone of the muscle the reconstituted preparation in an amount sufficient to diminish spasm and involuntary contraction while permitting voluntary muscle stimulation.
11. A method of decreasing tremor, rigidity, or spasticity in a muscle of a patient, the method comprising the steps of reconstituting the frozen, dried preparation of claim 1 and injecting into at least a portion of an innervation zone of the muscle the reconstituted preparation in an amount sufficient to diminish tremor, rigidity, or spasticity while permitting voluntary muscle stimulation.
12. A frozen, dried, sodium-chloride-free botulinum toxin preparation which, when reconstituted in aqueous media, retains greater than 75% of its regional chemodenervating activity.
13. The toxin preparation of claim 12 which, when reconstituted in aqueous media, retains greater than 90% of its activity.
14. A method of preparing a storage stabilized botulinum toxin pharmaceutical preparation comprising the step of:
freeze drying a purified toxin in a sodium chloride-free aqueous solution having a pH between 5.0 and 7.3, and containing a stabilizing protein as an excipient.
15. The method of claim 14 wherein said aqueous solution comprises phosphate buffer.
16. The preparation of claim 12 which, prior to being frozen and dried, is dialyzed to remove salts.

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Document Number 7

Entry 7 of 8 File: USPT Sep 23, 1997

US-PAT-NO: 5670484
DOCUMENT-IDENTIFIER: US 5670484 A

TITLE: Method for treatment of skin lesions associated with cutaneous cell-proliferative disorders
DATE-ISSUED: September 23, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Binder; William J.	Pacific Palisades	CA	90272	N/A

US-CL-CURRENT: 514/14; 514/2

CLAIMS:

The invention claimed is:
1. A method for mitigating or inducing remission of a skin lesion associated with a cutaneous cell-proliferative disorder in a mammal comprising administering a therapeutically effective amount of a Botulinum toxin in a pharmaceutically safe form to the mammal by delivery of the Botulinum toxin to the site of the lesion.
2. The method according to claim 1 wherein the Botulinum toxin is administered by subcutaneous injection.
3. The method according to claim 1 wherein the Botulinum toxin is Botulinum toxin A.
4. A method for controlling symptoms associated with the onset or presence of a cutaneous cell-proliferative disorder in a mammal comprising administering a therapeutically effective amount of a Botulinum toxin in a pharmaceutically safe form to the mammal by delivery of the Botulinum toxin to the mammal's skin.
5. A method for mitigating or inducing remission of a skin lesion associated with a cutaneous cell-proliferative disorder in a mammal comprising administering a therapeutically effective amount of a Tetanus toxin in a pharmaceutically safe form to the mammal by delivery of the Tetanus toxin to the site of the lesion.
6. The method according to claim 5 wherein the Tetanus toxin is administered by subcutaneous injection.
7. A method for mitigating or inducing remission of a skin lesion associated with a cutaneous cell-proliferative disorder in a mammal comprising administering a therapeutically effective amount of a biologically active fragment of a Tetanus toxin in a pharmaceutically safe form to the mammal by delivery of the Tetanus toxin to the site of the lesion.
8. The method according to claim 7 wherein the biologically active fragment is the lbc fragment of the Tetanus toxin.
9. A method for controlling symptoms associated with the onset or presence of a cutaneous cell-proliferative disorder in a mammal comprising administering a therapeutically effective amount of a Tetanus toxin in a pharmaceutically safe form to the mammal by delivery of the Tetanus toxin to the mammal's skin.

Document Number 8

Entry 8 of 8 File: USPT Apr 30, 1996

US-PAT-NO: 5512547
DOCUMENT-IDENTIFIER: US 5512547 A

TITLE: Pharmaceutical composition of botulinum neurotoxin and method of preparation
DATE-ISSUED: April 30, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Johnson; Eric A.	Madison	WI	N/A	N/A
Goodnough; Michael C.	Madison	WI	N/A	N/A

US-CL-CURRENT: 514/21; 514/2, 530/350, 530/363, 530/364, 530/825

CLAIMS:

We claim:
1. A pharmaceutical composition consisting essentially of:
(a) isolated, essentially pure type A botulinum neurotoxin;
(b) serum albumin; and
(c) an effective amount of trehalose which stabilizes the neurotoxin and improves the shelf life of composition so that it is stable at temperatures up to about 37.degree. C.
2. A composition of claim 1 in which the botulinum neurotoxin has specific toxicity of about 80 U/ng to about 96 U/ng.
3. A lyophilized pharmaceutical composition of type A botulinum neurotoxin which is stable for up to four months at about 37.degree. C. without the neurotoxin losing its potency, said composition consisting essentially of pure type A botulinum neurotoxin and an effective amount of trehalose to stabilize the neurotoxin.